IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Axel RIEDEL, et al.	:	
	:	Examiner: Leslie A. Royds
Serial No.: 10/757,015	:	Group Art Unit: 1614
Filed: January 14, 2004	:	

For: PHARMACEUTICAL COMBINATION FOR THE PREVENTION OR TREATMENT OF CARDIOVASCULAR, CARDIOPULMONARY, PULMONARY, OR RENAL DISEASES

APPEAL BRIEF

Mail Stop: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the decision of the Examiner finally rejecting claims 1 and 8-35 of the above-identified application.

(i) REAL PARTY IN INTEREST

The real party in interest herein is Boehringer Ingelheim International GmbH.

(ii) RELATED APPEALS AND INTERFERENCES

An appeal in application, Ser. No. 10/757,295, is being made in parallel with this appeal. While the claims between the two applications do not overlap in scope, the issues addressed in the two appeals are nearly identical and they have been prosecuted in parallel before the same Examiner. A Brief is being filed in Ser. No. 10/757,295 concurrently with this Brief.

(iii) STATUS OF THE CLAIMS

Claims rejected:	Claims 1 and 8-35.
Claims allowed:	(none)
Claims canceled:	Claims 2-7.

Claims withdrawn: (none)

Claims on Appeal: Claims 1 and 8-35 (Copy of claims on appeal in attached Appendix).

(iv) STATUS OF AMENDMENTS

No amendments after the Final Rejection have been proposed by Appellants.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention (independent claim 1) is directed to a method for the prevention or treatment of asthma, bronchitis, interstitial lung disease, insulin resistance, prediabetes, type 2 diabetes mellitus, metabolic syndrome, hypertension combined with hyperlipidaemia, or hypertension combined with atherosclerosis in a human or mammal patient in need thereof (see, e.g., page 1, lines 12-18, page 9, lines 4-15, and page 15, lines 1-27, of the instant specification). The method comprises administering a pharmaceutical composition to the patient comprising telmisartan or a salt thereof and simvastatin (see, e.g., page 1, lines 16-18, of the instant specification).

Appellants' invention (independent claim 18) is directed to a pharmaceutical composition, comprising telmisartan or a salt thereof and simvastatin (see, e.g., page 1, lines 18-23, of the instant specification).

Appellants' invention (independent claim 19) is directed to a pharmaceutical composition comprising: (a) telmisartan or salt thereof; (b) simvastatin; and (c) a pharmaceutically acceptable excipient or carrier (see, e.g., page 1, lines 18-23, and page 17, lines 18-26, of the instant specification).

Appellants' invention (independent claim 20) is directed to a pharmaceutical composition consisting essentially of: (a) telmisartan or salt thereof; (b) simvastatin; and (c) a pharmaceutically acceptable excipient or carrier (see, e.g., page 1, lines 18-23, and page 17, lines 18-26, of the instant specification).

Appellants' invention (independent claim 29) is directed to a pharmaceutical composition consisting essentially of: (a) telmisartan or salt thereof; (b) simvastatin; (c) a diuretic; and (d) a pharmaceutically acceptable excipient or carrier (see, e.g., page 1, lines 18-23, page 17, lines 18-26, page 11, lines 11-17, and original claim 29, of the instant specification).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following outstanding grounds of rejection are requested to be reviewed on appeal. For each ground, any separate consideration of the claims subject to that rejection is indicated.

1. The rejection of claims 1 and 8-17, on appeal, under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

2. The rejection of claims 1 and 8-35, on appeal, under 35 U.S.C. §103, as allegedly being obvious over the combined teachings of DeGasparo (WO 01/76573) in light of Robl (US Pat. Pub. No. 2002/001334) in view of Cecil's Textbook of Medicine ("Cecil"), Harlan (US Pat. Pub. No. 2001/0006656) and Bohm (WO 02/15891).

3. The provisional rejection of claims 1 and 8-35, on appeal, for obviousness-type double patenting over claims 2 and 7-18 of US Ser. No. 10/757,0295 in view of Harlan (US Pat. Pub. No. 2001/0006656).

4. The provisional rejection of claims 1 and 9-13 and 18-35, on appeal, for obviousness-type double patenting over claims 1-10, 12-15 and 18-25 of US Ser. No. 10/899,784.

5. The provisional rejection of claims 1, 8, 14-19 and 21-35, on appeal, for obviousness-type double patenting over claims 1-21 of US Ser. No. 11/300,947 in view of Drug Facts and Comparisons (1996).

(vii) ARGUMENT

1. Claims 1 and 8-17, on appeal, are adequately enabled to one of ordinary skill in the art, thus, the rejection under 35 U.S.C. §112, first paragraph, should be reversed.

The Final Office action acknowledges that the methods of "treating" the recited conditions are adequately enabled under 35 U.S.C. §112, first paragraph. The rejection is

made due to the inclusion in the claim scope also of methods of "preventing" the recited conditions. Due to the vagaries of physiology and variation in diagnostic thresholds, the line between what is considered treating and what is considered preventing is not a bright line. This vagary has particular applicability to the instant invention because the specification makes clear that one aspect of the invention is providing the ability to treat patients before they may be officially diagnosed with the stated condition. For example, see, e.g., page 1, lines 12-16; page 6, lines 24-26; page 9, lines 4-9; page 10, lines 17-22; page 11, lines 6-11 and elsewhere, discussing the ability to use the method to treat "first indications" of the conditions, pre-diabetes or patients "suspected of" the conditions. Further, it is also clear that an aspect of the invention is treating patients based on observance of certain physiological parameters (see, e.g., claims 9-13 on appeal) even absent an official diagnosis of the condition (see also page 10, lines 17-22). Thus, in order to properly claim their invention it is necessary in this context for applicants to claim a method for "prevention or treatment" of the recited conditions. It is believed to be clear that the specification teaches one of ordinary skill in the art how to provide and administer the compositions (see the discussion of the "Amount of Direction" Wands factor below). For the reasons stated above, it may not be easy to characterize this act of administering as being prevention or treatment, thus, the need for claiming the scope encompassing both possibilities. The grounds for rejection leave the impression that appellants claims are directly solely to prevention and are directed to providing an absolute cure to the conditions (see the Office action mailed March 30, 2006, paragraph bridging pages 7-8). Appellants' specification in context here, however, makes clear that this is not the meaning of the prevention term but that it is used – together with the treatment term – as a means to cover the invention when the line between the two is not clear.

The rejection is based largely on an interpretation that the term "prevention" requires that the method result in 0% occurrence of the condition and a guarantee that the condition would never develop. Reading the specification as a whole, however, appellants maintain that this is an unreasonable interpretation of the term. For one, this interpretation ignores that the claims recite "prevention or treatment" and thus encompass instances where the condition may be prevented in some instances, partially ameliorated in other instances, or treated after the fact in other instances. Additionally, this interpretation ignores the context in which the term is used in the specification. As described above, the "prevention" term is used in the specification in the context of the timing of administering the method, i.e., encompassing the possibility of conducting the method before the condition is fully diagnosed. It is not used in

the specification in the context of providing an absolute 100% cure of the condition, as alleged in support of the rejection. There is no basis from the specification to support the PTO's interpretation of the "prevention" term.

It is in this context that appellants cited the *Ex parte Cho*, Appeal No. 2001-2646 (Bd. Pat. App. & Int. 2002) decision (copy attached). *Cho* also addressed the issue of enablement of claims which encompassing "preventing" and "treating." The Examiner's rejection indicated that the claim scope encompassing treating was enabled but the inclusion of preventing supported a non-enablement rejection. Thus, the case is directly on point with the facts in the instant case. The Board reversed the Examiner's rejection stating (page 7):

> "Logically, if the recited compounds are useful for treating conditions such as pain and inflammation once they exist, they would also be expected to be effective in preventing pain and inflammation, if they were administered before the onset of pain or inflammation. The examiner has provided no reasoning to support a contrary conclusion" (**emphasis in original**).

The same logic applies here and the examiner has also provided no reasoning to support a contrary conclusion here.

It is alleged in the Final Office action that appellants failed to point out how the facts of *Cho* could be considered similar to those in the instant case because *Cho* related to different compounds for different uses. As the quote above makes clear, the conclusion in *Cho* was based on general logic, not the nature of the specific compounds and uses. The same general logic applies here. Further, the Examiner indicated in the Final Office action that there was no reason apparent why the *Cho* decision is particularly compelling with regards to the instant case and noted that it was a non-precedential opinion. Appellants fail to see how the decision could not be considered particularly compelling when it addresses the exact same issue on point here under non-distinguishing facts. Further, the non-precedential nature of the opinion does not refute its clear logic. Whether precedential or non-precedential, the point of law is well taken and highly applicable to the instant case.

Applicants submit that the above discussion provides sufficient reasons for reversing the rejection.

Additionally, the Wands factors (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed.Cir. 1988)) are discussed below as further proof of the adequate enablement of the claims on appeal.

The Breadth of the Claims – The breadth of claims, on appeal, is quite narrow. The claims are directed to methods for treatment or prevention of a specified group of nine related

conditions using a highly specific composition which combines two specific active agents. The narrow breadth of the claim strongly supports adequate enablement.

The Nature of the Invention – There has been no allegation in the Office actions of how the nature of the invention supports lack of enablement. In the absence of any apparent reason why the nature of the invention supports lack of enablement, this factor also must be considered as supporting a finding of enablement.

The Level of One of Ordinary Skill in the Art – The level of skill of one of ordinary skill in the art providing pharmaceutical compositions and methods for treating life-threatening conditions in humans is very high. The level of skill in this art would generally be that of a Ph.D. research chemist with years of experience. This high skill level strongly supports a finding of enablement.

The State of the Prior Art and Level of Unpredictability in the Art – The standard for enablement is not absolute predictability but only reasonable expectation of success; see *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510,1512 (Fed.Cir. 1993). On this issue, the only evidence the PTO has relied on to support the case for lack of enablement is the Grundy ("Metabolic Complications of Obesity") article. The article is relied on for its statement that treating or preventing the metabolic syndrome condition (one of the conditions recited in the claims) is "complex" (see, e.g., page 3 of the Final Office action). In fact, Grundy does not state that treating or preventing this condition is complex. Instead, the article is directed specifically to the role obesity plays in the condition and states that the "mechanistic link between insulin resistance and metabolic syndrome is complex" (see the abstract of Grundy). The article then goes on to describe in great detail how the metabolic syndrome condition is characterized and how a number of factors affect the condition. Thus, while acknowledging the complexity, it also acknowledges that much is known about the causes and many aspects of the condition. The fact that the condition may be complex does not support lack of enablement when – although complex – it is well understood by one of ordinary skill in the art. The grounds of rejection fail to explain why the complexity of the condition supports that one of ordinary skill in the art could not carry out the claimed method given the high level of knowledge in the art and direction given in the disclosure of the details of administering the compositions to carry out the method. Given that the claimed method of treatment of metabolic syndrome is admitted to be enabled, it would follow that the method of prevention of metabolic syndrome would also be enabled regardless of the alleged "complex" nature of the syndrome. As discussed above, the difference in carrying out the method of treatment or

prevention is merely one of timing. The Grundy article also states (abstract) that "at the heart of metabolic syndrome is insulin resistance." This fact closely ties the method of treating or preventing this condition with the method of treating or preventing the other conditions to which the claimed methods are directed, e.g., insulin resistance, prediabetes and type 2 diabetes. The PTO has not provided any evidence or argument that treating or preventing these other conditions is not enabled. But the close tying of metabolic syndrome with these conditions would support that, if treating or preventing the other conditions is enabled, then treating or preventing metabolic syndrome would also be. The abstract of the Grundy article concludes that a "better understanding of the molecular basis of this relationship [i.e., the mechanistic link between insulin resistance and metabolic syndrome] is needed." Again, this statement relates only to this particular relationship. Further, the fact that a journal article concludes that a better understanding is needed does not prove that one of ordinary skill in the art could not carry out methods to treat the condition. Journal articles usually conclude in this manner because researchers are always looking for a better understanding. This does not evidence that the current understanding is insufficient for one of ordinary skill in the art to carry out methods to treat the condition. Obviously, researchers are always searching for improved ways to treat conditions despite that existing methods for treating them may already be well known. Appellants additionally point out that the principle and closest prior art reference cited in the obviousness rejection, DeGasparo also recites that its methods are for prevention or treatment of the conditions recited there (see page 1, line 8). Thus, this closest prior art is consistent with appellants' position that this specific art area is directed to treatment and prevention of the conditions.

The Amount of Direction Provided – The specification provides a great deal of guidance on how to carry out the claimed invention, including for the prevention aspect. The discussion in the first paragraph above for this issue is referred to, pointing out that the specification makes clear that aspects of the invention include providing the ability to treat patients before they may be officially diagnosed with the stated condition, to treat "first indications" of the conditions, pre-diabetes or patients "suspected of" the conditions, and further, treating patients based on observance of certain physiological parameters even absent an official diagnosis of the condition. The disclosure thus addresses methods encompassing the spectrum spanning preventing and treating the stated conditions. Furthermore, the specification provides a great deal of guidance on how to administer the specifically identified compositions that result in the method. For example, pages 8-13 and 17-23 of the

specification give a wealth of information on assays for assessing the desired activity of the compositions, physiological parameters for identifying patients in need of the method, manners of formulating the compositions, suitable methods for administering the compositions and specific doses of the active agents in the compositions. From such guidance, one of ordinary skill in the art – who is of a very high skill level – can routinely carry out the claimed invention.

The Existence of Working Examples – It is well established that no working examples are required to establish enablement; see, e.g., *In re Borkowski*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970); and *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). This is commonly the case for medical treatment methods where clinical work is not performed until later in the development path.

The Quantity of Experimentation Needed – The requirement for some experimentation – even a large amount – does not equate to **undue** experimentation or lack of enablement. Where the experimentation required is merely routine to one of ordinary skill in the art, it is not undue experimentation and does not support a case for lack of enablement. See, e.g., *Wands*, at 8 USPQ2d at 1404, stating: "Enablement is not precluded by the necessity for some experimentation ... . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation'." See also *Ex parte Jackson*, 217 USPQ 804 (Bd. Pat. App. 1982), stating: "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." As stated above, the experimentation needed by the highly skilled one of ordinary skill in the art here would only be routine.

Considered as a whole, appellants urge that the Wands factors clearly support that the claims are reasonably enabled.

For the above reasons, it is urged that the specification, read in light of the knowledge available to one of ordinary skill in the art, provides an adequate disclosure or how to make and use the invention of the claims on appeal. Thus, the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement should be reversed.

2. Claims 1 and 8-35, on appeal, are not obvious obvious to one of ordinary skill in the art from the combined teachings of DeGasparo (WO 01/76573) in light of Robl (US Pat. Pub. No. 2002/001334) in view of Cecil's Textbook of Medicine ("Cecil"), Harlan (US Pat. Pub. No. 2001/0006656) and Bohm (WO 02/15891), thus, the rejection under 35 U.S.C. §103 should be reversed.

DeGasparo provides a broad generic teaching regarding compositions combining any two of: (i) an AT_1-receptor optionally with a diuretic, (ii) a HMG-Co-A reductase inhibitor and (iii) an ACE inhibitor, for use in the prevention or treatment of a number of conditions including insulin resistance, syndrome X (prediabetes), type 2 diabetes mellitus, hypertension, hyperlipidaemia, and atherosclerosis; see, e.g., page 1, first paragraph. Thus, DeGasparo generically encompasses the following options for combinations:

(a) AT_1 receptor antagonist + HMG-Co-A reductase inhibitor;

(b) AT_1 receptor antagonist + ACE inhibitor

(c) AT_1 receptor antagonist + HMG-Co-A reductase inhibitor + ACE inhibitor;

(d) AT_1 receptor antagonist + diuretic + HMG-Co-A reductase inhibitor;

(e) AT_1 receptor antagonist + diuretic + ACE inhibitor;

(f) AT_1 receptor antagonist + diuretic + HMG-Co-A reductase inhibitor + ACE inhibitor; and

(g) HMG-Co-A reductase inhibitor + ACE inhibitor.

As for the AT_1 receptor antagonist DeGasparo discloses a number of examples of them in the paragraph bridging pages 3-4. This list includes telmisartan but it is not indicated as a preferred selection. To the contrary, valsartan is indicated as the preferred selection; see, e.g., page 4, first full paragraph. As for the HMG-Co-A reductase inhibitor, DeGasparo provides a list of examples at page 5, second paragraph, which includes simvastatin. DeGasparo discloses preferred combinations from the paragraph bridging pages 5-6 thru the second full paragraph of page 6. In every preferred combination which includes an AT_1 receptor antagonist, it is always valsartan.

DeGasparo does not provide any teaching of the specific combination of telmisartan and simvastatin. DeGasparo does not provide any specific teaching to combine telmisartan in particular with any other component. When combining AT_1 receptor antagonists for its compositions, DeGasparo always points specifically to valsartan as the selection for this component. Thus, DeGasparo directs one of ordinary skill in the art to the selection of

valsartan rather than telmisartan. Simvastatin is mentioned more prominently in DeGasparo but not in combination with telmisartan, only with valsartan.

Despite the broad generic disclosure of DeGasparo, there is no fair teaching directing one of ordinary skill in the art to the specific combination of telmisartan and simvastatin. To arrive at such a specific combination, one of ordinary skill in the art would have to make a number of selections out of the generic disclosure of DeGasparo and the reference fails to provide blazemarks for one of ordinary skill in the art to make such selections. First, from the list of choices of possible general combinations (a) to (g) above encompassed by DeGasparo, one would have to select a combination which includes an AT_1 receptor antagonist + HMG-Co-A reductase inhibitor. Second, one would have to select telmisartan as the specific AT_1 receptor antagonist and ignore the direction from DeGasparo to select valsartan. Third, one would have to select simvastatin as the HMG-Co-A reductase inhibitor. De Gasparo does not provide a fair suggestion for one of ordinary skill in the art to make all of the selections in combination. As was clearly set forth in *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992), it is not the law that "regardless of how broad, a disclosure of a chemical genus renders obvious any species which happens to fall within it." Instead, the disclosure must be considered as a whole as to whether it fairly suggests the claimed invention to one of ordinary skill in the art; see also *In re Baird*, 29 USPQ2d 1550 (Fed. Cir. 1994). Appellants urge that, despite the broad generic teachings of DeGasparo, it does not provide a fair suggestion to make the selections necessary from within this broad disclosure to arrive at the very specific selection invention of the claims on appeal.

The secondary references of Robl, Cecil, Harlan, or Bohm fail to provide teachings which make up for the deficiency of DeGasparo to fairly suggest applicants' specific combination or provide a reason for one of ordinary skill in the art to modify DeGasparo to provide such a specific combination. Robl is directed to HMG-CoA reductase inhibitor compounds distinct from simvastatin; see, e.g., page 16, para. [0166]. Robl teaches that their new HMG-CoA reductase inhibitors can be combined with known ones, such as simvastatin; see, e.g., page 16, para. [0168]. But it gives no suggestion of combining simvastatin with any other actives, particularly not telmisartan. Harlan teaches aerosol formulations of statins. Such formulations are not intended to combine a statin such as simvastatin with an antihypertensive, much less with telmisartan. Bohm teaches combining telmisartan with the ACE inhibitor ramipril, i.e., to two active ingredients acting on the renin-angiotensin system. It provides no suggestion to combine telmisartan with a HMG-CoA reductase inhibitor,

particular simvastatin. Cecil has no teachings relating to telmisartan or simvastatin or their combination.

Thus, DeGasparo taken together in combination with all of the secondary references still fails to fairly suggest the claimed invention to one of ordinary skill in the art. Thus, appellants urge that no prima facie case of obviousness has been established. Alternatively, appellants urge that, if any prima facie case of obviousness is established by the references, it is a weak case for the reasons stated above. And such weak case for obviousness is readily overcome by the evidence of unexpected results discussed below.

The nonobviousness of the claimed invention, however, is clearly and convincingly shown by the evidence of significant advantages of the combination of telmisartan and simvastatin which could not have been expected by one of ordinary skill in the art.

Appellants invention is based in part on the surprising advantage of using – specifically – the AT_1 receptor antagonist telmisartan in combination with simvastatin. It has been discovered that telmisartan – in addition to its expected activity for reducing blood pressure – also increases the expression of genes whose transcription is known to be regulated by the PPARgamma receptor; see, e.g., page 8, line 1, to page 9, line 2, of the instant specification. As discussed in the specification, this additional activity makes telmisartan particularly advantageous to combine for use in methods where an anti-diabetic activity is desired, i.e., for treating or preventing the conditions recited in the claims on appeal. This additional advantageous activity was particularly surprising because other AT_1 receptor antagonists do not exhibit such activity or do so only to a significantly lower extent. Example 3, pages 27-29, of the instant specification provides data showing that telmisartan has particularly potent activity on the PPARgamma pathway in the PPARgamma reporter cll line, while the activity of two other AT_1 receptor antagonists is of a significantly lesser extent. Reference is also made to the Benson (*Hypertension*, May 2004, pp. 993-1002) and Pershadsingh (*Diabetes Care: Observations*, Vol. 27, No. 4, April 2004, p. 1015) articles (copies provided) which are not prior art. (These articles are not of record in this application but were in the related case, Ser. No. 10/757,295, whose prosecution and appeal has run in parallel with the same Examiner; appellants urge that they be considered here as well since they merely confirm what is already taught in appellants' specification). These articles further confirm this advantageous PPARgamma modulating activity for telmisartan, that such activity is exhibited uniquely by telmisartan and not other AT_1 receptor antagonists and that it makes telmisartan particularly advantageous for treating conditions such as metabolic

syndrome, diabetes and cardiovascular conditions; see particularly the Abstract of Benson stating:

> "None of the other commercially available angiotensin II receptor antagonists appeared to activate PPARγ .. In contrast to ordinary antihypertensive and antidiabetic agents, molecules that can simultaneously block the angiotensin II receptor and activate PPARγ have the potential to treat both hemodynamic and biochemical features of the metabolic syndrome and could provide unique opportunities for the prevention and treatment of diabetes and cardiovascular diseases."

These data provide a clear and convincing showing that the selection – specifically -- of telmisartan from among AT_1 receptor antagonists in general for combination with simvastatin provides a significant, surprising and unexpected advantage for treating or preventing the conditions recited in the claims on appeal. This unexpected advantage provides strong proof of the nonobviousness of appellants' selection invention directed to the specific combination of telmisartan and simvastatin. See also, page 13, line 23, to page 14, line 13, and page 17, lines 4-18, of the instant specification describing why this advantage of telmisartan provides a particular useful result when combined with simvastatin.

The cited DeGasparo, Robl, Cecil, Harlan and Bohm references fail to provide any suggestion whatsoever that telmisartan increases the expression of genes regulated by the PPARgamma receptor. The references also fail to provide any teaching which would give one of ordinary skill in the art any reasonable expectation that telmisartan would be particularly advantageous in comparison to other AT_1 receptor antagonists for any use, particularly when used in combination with simvastatin. Indeed, De Gasparo directs one of ordinary skill in the art towards the use of the distinct AT_1 receptor antagonist valsartan over telmisartan. Bohm indicates a preference to telmisartan but only when in combination with ACE inhibitors. Bohm provides no suggestion of the advantageous PPARgamma modulating activity for telmisartan or any advantage when used in combination with simvastatin or for treating or preventing the conditions recited in the claims on appeal.

Appellants respectfully submit that the evidence of provides a clear and convincing case of the unexpected results of the selection invention of the claims on appeal and overcomes any prima facie case of obviousness established by the cited references.

For all of the above reasons, it is urged that the combined teachings of the prior art, viewed as a whole together with the evidence of unexpected results, fail to render the invention of the claims on appeal obvious to one of ordinary skill in the art. Thus, the

rejection under 35 U.S.C. §103 should be reversed.

3. Claims 1 and 8-35, on appeal, are not obvious variants of claims 1 and 8-35 of US Ser. No. 10/757,295 in view of Harlan (US Pat. Pub. No. 2001/0006656), thus, the provisional rejection for obviousness-type double patenting should be reversed.

The claims of the '295 application are directed to compositions containing telmisartan and atorvastatin and methods for using them. The instant claims are directed to compositions containing telmisartan and simvastatin and methods for using them. Thus, the compositions and methods between the two claims are not overlapping and are mutually exclusive, i.e., one requires atorvastatin and not simvastatin and the other vice versa. As shown in Fig. 13 of the cited Harlan reference, the chemical structures of atorvastatin and simvastatin are very different. Thus, clearly the same invention is not being claimed between the two applications and appellants are not attempting to obtain two patents encompassing the same subject matter.

It is alleged in support of the rejection (see the Office action of March 30, 2006, page 23) that it would have been obvious to exchange atorvastatin and simvastatin because Harlan teaches (page 2, para. [0025]) that atorvastatin and simvastatin were known to have "the same inhibitory effect on HMG-CoA reductase." Appellants respectfully submit that Harlan does not teach that the two compounds have the "same inhibitory effect." Harlan teaches that both of the compounds are known as HMG-CoA reductase inhibitors but there is no basis to allege that they provide the same inhibitory effect. In view of the very different chemical structures of the compounds and the absence of any teaching on the record that they have the same inhibitory activity, appellants urge that one of ordinary skill in the art could have no reasonable expectation that atorvastatin and simvastatin would exhibit the same or even similar effect. They both would be expected to have some manner of HMG-CoA reductase inhibiting effect. However, the record does not support that one of ordinary skill in the art would reasonably expect that you could exchange the two compounds in a composition with telmisartan and get the same or similar results. Thus, there is no basis to allege the compositions and methods using them would be obvious variants.

For the above reasons, the provisional rejection for obviousness-type double patenting should be reversed.

4. Claims 1 and 9-13 and 18-35, on appeal, are not obvious variants of claims 1-10, 12-

15 and 18-25 of US Ser. No. 10/899,784, thus, the provisional rejection for obviousness-type double patenting should be reversed.

The claims of the '784 application have been amended since the original rejection based thereon was made (see the Office action of March 31, 2006, pages 24-25). With one exception (see below), the claims of the '784 application are directed to compositions containing telmisartan and amlopidine and methods for using them. The instant claims are directed to compositions containing telmisartan and simvastatin and methods for using them. Thus, the compositions and methods between the two claims are not overlapping and are mutually exclusive, i.e., one requires simvastatin and not amlopidine and the other vice versa. The chemical structures of amlopidine and simvastatin are very different. Thus, clearly the same invention is not being claimed between the two applications and appellants are not attempting to obtain two patents encompassing the same subject matter.

The basis for the rejection (see the Office action of March 30, 2006, pages 24-25) that the claimed inventions overlap is not applicable to these claims. Further, there is no basis on the record to support that it would have been obvious to exchange simvastatin and amlopidine. In view of the very different chemical structures of the compounds and the absence of any teaching on the record that they have the same or similar activity, appellants urge that one of ordinary skill in the art could have no reasonable expectation that simvastatin and amlopidine would exhibit the same or even similar effect. Thus, there is no basis to allege the compositions and methods using them would be obvious variants.

For the above reasons, this provisional rejection for obviousness-type double patenting should also be reversed.

It is noted that claim 18 of the '784 application is broader and does encompass the embodiment of a composition combining telmisartan and simvastatin (though not methods of using such compositions). However, this claim was restricted and is currently withdrawn from prosecution in the '784 application. It is likely this claim would not be retained in any patent resulting from the '784 application but, if it is, it will be addressed with a terminal disclaimer.

5. Claims 1, 8, 14 and 21-35, on appeal, are not obvious variants of claims 1-21 of US Ser. No. 11/300,947 in view of Drug Facts and Comparisons (1996), thus, the provisional rejection for obviousness-type double patenting should be reversed.

The claims of the '947 application are directed to compositions containing telmisartan

and hydrochlorothiazide and methods for using them. The instant claims are directed to compositions containing telmisartan and simvastatin and methods for using them. Thus, the compositions and methods between the two claims are not overlapping and are mutually exclusive, i.e., one requires hydrochlorothiazide and not simvastatin and the other vice versa. Claims 17 and 18, on appeal, recite the additional inclusion of a diuretic which may be hydrochlorothiazide. But even these claims are not overlapping with the '947 claims since the '947 claims do not recite inclusion of simvastatin. The chemical structures of hydrochlorothiazide and simvastatin are very different. Thus, clearly the same invention is not being claimed between the two applications and appellants are not attempting to obtain two patents encompassing the same subject matter.

It is alleged in support of the rejection (see the Office action of March 30, 2006, page 26) that the instant claims (actually only claims 27-35) recited a composition comprising telmisartan and a diuretic such as hydrochlorothiazide, which is the same invention claimed in the '947 application. This argument, however, ignores the requirement in the instant claims on appeal that the compositions contain simvastatin. The '947 claims give no hint whatsoever to compositions containing simvastatin – or anything similar. Appellants urge that one of ordinary skill in the art could have no reasonable expectation that a composition containing telmisartan and hydrochlorothiazide would exhibit the same or similar effect as such a composition which additionally contains the active agent simvastatin. The record does not support that one of ordinary skill in the art would reasonably expect that you could add such a further active agent and get the same or similar results. Thus, there is no basis to allege the compositions and methods using them would be obvious variants.

For the above reasons, this provisional rejection for obviousness-type double patenting should also be reversed.

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims 1 and 8-35, on appeal, is in error and should be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: 01-1443

Date: November 9, 2009

(viii) CLAIMS APPENDIX

1. A method for the prevention or treatment of asthma, bronchitis, interstitial lung disease, insulin resistance, prediabetes, type 2 diabetes mellitus, metabolic syndrome, hypertension combined with hyperlipidemia, or hypertension combined with atherosclerosis in a human or mammal patient, the method comprising administering to the patient in need thereof an effective amount of:

(a) telmisartan or salt thereof; and

(b) simvastatin.

8. The method according to claim 1, wherein the patient is a human.

9. The method according to claim 8, wherein the patient has a fasting blood sugar level more than 110 mg of glucose per dL of plasma.

10. The method according to claim 8, wherein the patient has a blood level for triglyceride more than 150 mg/dL.

11. The method according to claim 10, wherein the patient is a female and has a blood level for HDL less than 40 mg/dL of plasma.

12. The method according to claim 10, wherein the patient is a male and has a blood level for HDL less than 50 mg/dL of plasma.

13. The method according to claim 6, wherein the patient has a systolic blood pressure greater than 130 mmHg and a diastolic blood pressure greater than 80 mmHg.

14. The method according to claim 11, wherein the simvastatin is administered in a daily dose of about 0.009 mg/kg body weight to 6.43 mg/kg body weight by oral route and the telmisartan or salt thereof is administered in a daily dose of about 0.143 mg/kg to 7.143 mg/kg body weight by oral route.

15. The method according to claim 12, wherein the simvastatin is administered in a daily

dose of about 0.009 mg/kg body weight to 6.43 mg/kg body weight by oral route and the telmisartan or salt thereof is administered in a daily dose of about 0.143 mg/kg to 7.143 mg/kg body weight by oral route.

16. The method according to claim 11, wherein the simvastatin is administered in a daily dose of about 0.286 mg/kg body weight by parenteral route and the telmisartan or salt thereof is administered in a daily dose of about 0.286 mg/kg body weight by parenteral route.

17. The method according to claim 12, wherein the simvastatin is administered in a daily dose of about 0.286 mg/kg body weight by parenteral route and the telmisartan or salt thereof is administered in a daily dose of about 0.286 mg/kg body weight by parenteral route.

18. A pharmaceutical composition comprising:

(a) telmisartan or salt thereof; and

(b) simvastatin.

19. A pharmaceutical composition comprising:

(a) telmisartan or salt thereof;

(b) simvastatin; and

(c) a pharmaceutically acceptable excipient or carrier.

20. A pharmaceutical composition consisting essentially of:

(a) telmisartan or salt thereof;

(b) simvastatin; and

(c) a pharmaceutically acceptable excipient or carrier.

21. The pharmaceutical composition according to claim 18, wherein the pharmaceutical composition contains 20 mg to 200 mg of telmisartan and 2.5 mg to 40 mg of simvastatin.

22. The pharmaceutical composition according to claim 19, wherein the pharmaceutical composition contains 20 mg to 200 mg of telmisartan and 2.5 mg to 40 mg of simvastatin.

23. The pharmaceutical composition according to claim 20, wherein the pharmaceutical

composition contains 20 mg to 200 mg of telmisartan and 2.5 mg to 40 mg of simvastatin.

24. The pharmaceutical composition according to claim 18, wherein the weight ratio of simvastatin to telmisartan or salt thereof is 1:2 to 1:16.

25. The pharmaceutical composition according to claim 19, wherein the weight ratio of simvastatin to telmisartan or salt thereof is 1:2 to 1:16.

26. The pharmaceutical composition according to claim 20, wherein the weight ratio of simvastatin to telmisartan or salt thereof is 1:2 to 1:16.

27. The pharmaceutical composition according to claim 18, further comprising a diuretic.

28. The pharmaceutical composition according to claim 19, further comprising a diuretic.

29. A pharmaceutical composition consisting essentially of:

(a) telmisartan or salt thereof;

(b) simvastatin;

(c) a diuretic; and

(d) a pharmaceutically acceptable excipient or carrier.

30. The pharmaceutical composition according to claim 27, wherein the diuretic is HCTZ or chlorthalidone.

31. The pharmaceutical composition according to claim 28, wherein the diuretic is HCTZ or chlorthalidone.

32. The pharmaceutical composition according to claim 29, wherein the diuretic is HCTZ or chlorthalidone.

33. The pharmaceutical composition according to claim 30, wherein the pharmaceutical composition contains 10 mg to 50 mg of HCTZ or chlorthalidone.

34. The pharmaceutical composition according to claim 31, wherein the pharmaceutical composition contains 10 mg to 50 mg of HCTZ or chlorthalidone.

35. The pharmaceutical composition according to claim 32, wherein the pharmaceutical composition contains 10 mg to 50 mg of HCTZ or chlorthalidone.

(ix) EVIDENCE APPENDIX

1. Decision in *Ex parte Cho*, Appeal No. 2001-2646 (Bd. Pat. App. & Int. 2002) – Cited by appellants in reply filed September 15, 2006 – Addressed by Examiner in Final Office action of June 5, 2009.

2. Benson (*Hypertension*, May 2004, pp. 993-1002) – Cited by Appellants in IDS filed August 16, 2004, in related Ser. No. 10/751,295.

3. Pershadsingh (*Diabetes Care: Observations*, Vol. 27, No. 4, April 2004, p. 1015) – Cited by Appellants in IDS filed August 16, 2004 in related Ser. No. 10/751,295.

(x) RELATED PROCEEDINGS APPENDIX

(None)